Excipients: A Regulatory Support Prospective

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Overview

- Justification
- Specific Dosage Forms
- Control Correspondences
- Special Considerations
- Summary

Justification

- Consults
  - Sent to Office of New Drugs (OND) for review with available pharm/tox information once acknowledged
  - May take two to three months for a review
- Review available internal databases
  - Inactive Ingredient Database
  - Original NDA or ANDA submissions

Justification cont.

- Products required to be Q1/Q2 may be within ±5% of an approved ingredient, but cannot exceed the highest amount within our databases
- Each inactive ingredient must be justified unless it is ≤0.1% of the total drug product weight
- Dose vs MDD justification

Statistics

- FY 2010 Received 813 RTR = 14%
- FY 2009 Received 859 RTR = 9%,
- FY 2008 Received 830 RTR = 15%
- FY 2007 Received 877 RTR = 11%
- FY 2006 Received 796 RTR = 8.5%

RTR = Refuse to Receive ANDAs

RTR Breakdown

(25) Bioequivalence requirement(s) not being met

(23) Clinical

(13) Packaging

(10) Inactive ingredient levels

(10) MISC – Micro, Container Closure, Batch Records, etc.

RTR Breakdown Cont.

(8) Stability
(7) Submission format
(5) Not Q1/Q2 – Ophthalmic
(4) Basis of Submission
(3) Not Q1/Q2 – Injection
(3) Not Q1/Q2 – Nasal and other
(2) Receipt date of DMF
(2) Multiple minor issues (between ~10-20 issues)

Solid Oral Dosage Forms

- Must be justified via the same route of administration as proposed product
  - i.e. Buccal, Sublingual, Oral
- Route may be influenced by absorption site
  - Orally Disintegrating Tablet
  - Some Buccal products
- “Generic” descriptions do not always justify an inactive
  - Inactive may be a different grade or different product

Oral Solutions

- Not required to be Quantitatively (Q1) or Qualitatively (Q2) the same as the RLD
- Eligible for Bio Waiver under 21 CFR 320.22(b)(3)
- Be aware of the amounts of some inactive ingredients
  - Sugar Alcohols (Sorbitol, Mannitol, Glycerin)
  - May cause a change in Bioavailability

Ophthalmics

- **Required** to be Q1 and Q2 with the RLD
- 21 CFR 314.94(a)(9)(iv) no longer applies
  - Determination that changes in the formulation may adversely affect the efficacy of the drug product
- If you decide to make any change to the preservative, buffer, tonicity adjuster, thickening agent

Ophthalmics cont.

- BE study must submitted at time of filing
- If no BE study is submitted we will Refuse to Receive your application
- 505(b)(2) option

Ophthalmics cont.

- Provide the amount of Benzalkonium Chloride as amount of Benzalkonium in the product
  - Ex: if using a 50% Benzalkonium Chloride solution, 0.5 mL would contain 0.25 mg of Benzalkonium
- When using a different hydrate of an inactive than in the RLD, provide the equivalent amount of the two inactives
  - Ex: Xdihydrate used in RLD = Xheptahydrate in generic

Topical Products

- Includes lotions, ointments, creams, solutions, foams , gels
- Generally, solutions do not need to be Q1/Q2 with the RLD under 21 CFR 320.22(b)(3)
  - Some products that fall under the Bioequivalence Waiver will still need to provide Bioequivalence and/or Clinical studies

Topical Products cont.

- Creams and Ointments do not need to be Q1/Q2 with the RLD
  - Not eligible for Bio Waiver
  - Will need to provide Clinical studies regardless

Topical Products cont

- Must demonstrate product is a solution when administered for some products to receive a Bio Waiver
  - Example: Foam

- Changes in amounts of inactive ingredients from the RLD may require additional studies or pharm/tox data

Nasal Sprays

- Must be Q1/Q2 with the RLD
- Still need to provide *in-vitro* studies
  - Plume geometry, droplet size, dispersion, etc.
- If the product is a suspension, will need to provide additional *in-vivo* studies

Metered Dose Inhaler (MDI) Nebulizer Solution

- MDI recommended to be Q1/Q2 with the RLD
- 21 CFR 314.94(a)(9)(v) allows for changes but must demonstrate changes do not affect safety or efficacy
- Products for nebulization are **not** required to be Q1/Q2 under 21 CFR 320.22(b)
- MDI's are not eligible for a waiver

Parenteral

- Q1/Q2 to the RLD is always preferred
- May make changes in the formulation under 21 CFR 314.94(a)(9)(iii)
  - Buffer, Preservative, Antioxidant
- pH adjusters **are not** considered exception excipients
  - If the RLD has pH adjusters in the labeling, they **must be** included in the generic formulation and production batch records even if they are not utilized
  - 21 CFR 201.100(a)(iii) does not require a parenteral to list pH adjusters in the labeling

Transdermals

- The most difficult products to justify inactive ingredient
  - Backing Film, Release Liners, Adhesives, etc.
  - Components rarely in our databases
- If the components have been used in a previously approved product, let us know
  - Provide DMF numbers and approved product NDA or ANDA number(s)

Control Correspondence (CC)

- Regulatory Support Branch has responded to 381 CC for FY 2010
- The current turnaround time is 60 days
- Limits will be place on CC in the near future regarding the amount of controls that can be submitted by one firm per year and the expected response time
- We no longer respond by e-mail to a CC. We will respond by telephone call

(CC) cont.

- We will not respond directly to CC from outside the US. Firms that are outside the US must submit their CC to OGD through their US Agent
- Do not send duplicate CC
- We have seen the same requests sent to the Generic Drugs e-mail account and the CDER DRUG INFO account or other means of submission
- Causes additional delays and confusion

(CC) cont.

- Provide all the required information with request
- Determination is made similar to a filing review justification
  - May include additional steps for justification such as requesting the original NDA submission from storage

(CC) cont.

- Do not send Pharm/Tox information. We will not pre-review this information
  - If we cannot justify your inactive ingredient, pharm/tox information will need to be submitted in the ANDA submission

- We will not review formulations other than for Q1/Q2 sameness

  - **Reminder - CC reviews are a courtesy extended to industry**

Percent Amount

- Issues may occur when using percentage to justify an inactive ingredient
  - Especially prevalent with Oral solutions, Parenterals and Topical Products

- Example: The IID states an inactive ingredient is used at an amount of 90%
  - Unable to determine from this if the ingredient is presented as weight/volume (w/v), weight/weight (w/w) or volume/volume (v/v) or if this is amount per container or per dose
  - **Always provide amounts in mg/mL whenever possible**

Pharmacology/Toxicology

- When in doubt, provide pharm/tox information in the original ANDA submission

- Must provide complete studies of the inactive ingredient *via* the same route of administration
  - No summaries or reference to locations of studies
  - If a DMF contains all the studies, provide copies of the studies, **do not** reference the DMF

Pharmacology/Toxicology cont.

- Submit pharm/tox information in **electronic format only**
  - If ANDA is paper, provide a separate CD
  - If electronic, provide an easily identifiable location or section
  - Paper copies of the pharm/tox information **will not** be acceptable
- Studies must use Rodent and Non-rodent subjects at a minimum
  - See Guidance for Industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients,* May 2005

Flavoring/Fragrance Ingredients or Agents

- The components and composition for these products must be provided at the time of submission
  - **Reference only to a DMF/LOA is not sufficient**
- Most flavorings and fragrances are not in the IID or the internal databases

Flavoring/Fragrance Ingredients or Agents cont.

- The applicant may provide the components and composition for only the portion of the formulation that is ≥ 0.1% of the total drug product weight
  - This also applies to Natural and/or Artificial components within the product formulation

Iron

- If an inactive ingredient contains an iron (ferric) component, the daily elemental iron intake must be taken into account
  - Occurs most often with coloring agents
- May not exceed 5 mg/day of elemental iron
  - 21 CFR 73.1200(c)
- Provide justification within the components and composition section (3.2.P.1) to demonstrate the daily amount does not exceed the daily limit

DMF

- May be used to provide the formulation certain inactives
- The DMF **must** be in electronic format, have been previously submitted to the Agency and must be up to date
- Need to specify where the formulation can be located in the DMF
- We will not review the DMF itself, only the formulation
- If we are unable to locate the formulation or searching through a DMF is too time consuming, we will request a copy of the inactive ingredient formulation components and composition
- Currently only in preliminary stages

Summary

- The more information at the time of submission, the better
- Develop internal inactive ingredient database
- Do your homework!
- If an inactive ingredient is accepted by Regulatory Support, either via an ANDA submission or a Control Correspondence, does not imply there will not be issues during any one of the Divisional reviews

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